REMARKS

Applicants respectfully request entry of the amendments hereinabove, reconsideration of the Office Action mailed on July 15, 2010 and allowance of the claims.

As an initial note to assist in the understanding of this Amendment and Response with respect to both 112 and 103, Applicants note Franson et al. is directed to formulations having HPC adsorbed (e.g., coated) on the NSAID particles. The HPC functions as a surface modifier that is adsorbed on the particles by a spray drying process. The resulting coating acts to inhibit agglomeration and ultimately to increase bioavailability. Applicants claims are simply not directed to HPC coated celebrex particulates.

35 U.S.C. §112, second paragraph

Claims 16 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The rejection states that claim 16 contains the trademark/trade name "Rexcel™". The rejection states that where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. §112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The rejection also states that the claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. The rejection states that a trademark or trade name is used to identify a source of goods, and not the goods themselves. The rejection also states that accordingly, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. The rejection states that in the present case, the trademark/trade name is used to identify/describe the diluents and, accordingly, the identification/description is indefinite.

The rejection states that there is no description in the specification of the exact ingredients of "Rexcel™" which can change over time.

Applicants have herein amended claim 16 in accordance with the Examiner's suggestion which obviates the 35 U.S.C. §112, second paragraph rejection. Applicants have done so in an effort to expedite prosecution without waiver or prejudice against refiling the original filed claims.

Claims 23 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The rejection states that claim 23 fails to further limit the subject matter of claim 1. The rejection states that while claim 1 precludes the presence of HPC, the binding agents recited in claim 23 include HPC.

Applicants traverse the rejection of claim 23 (as amended) under 35 U.S.C. §112, since claim 1 does not preclude the presence of HPC as currently amended. For example, claim 1 merely excludes HPC when it is adsorbed onto the particulate celecoxib (e.g., as a surface modifier coating). Thus Applicants formulation could have HPC in the formulation other than being adsorbed onto the particulate celecoxib.

35 U.S.C. §112, first paragraph

Claims 1-10, 12-50, 72-75, 84 and 86-90 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The rejection states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection states that while page 22, lines 20- 21 of the present specification discloses the use of hydroxypropylcellulose (HPC), the specification specifically teaches that such HPC is a binding agent particularly added for tablet formulations (See lines 10-11 of page 22). The examiner notes that claim 1 is not directed to a tablet formulation. The rejection also states that claim 1 does not require the presence of binding agent. The rejection reasons that this is evident by the limitation in claim 14, which recites that the composition *further* comprising binding agents. The rejection concludes that because claim 1 does not recite a tablet and binding agents as positive limitations, the claims cannot preclude the present of HPC.

Applicants traverse the rejection of claims 1-10, 12-50, 72-75, 84 and 86-90 under 35 U.S.C. §112, first paragraph, since these claims do not preclude the presence of HPC as currently amended.

First the relevance of HPC to claim 23 has been addressed above.

With respect to the rejection's remarks that claim 1 did not have binding agent as dependent claim 14 "further comprised binding agents" Applicants note that claim 14 has been amended to delete the modifier "further" preceding the recitation of the term "binding agents".

In addition, Applicants traverse the Rejection's remark that "claim 1 is not limited to a tablet formulation and that HPC is a binding agent particularly added for tablet formulations" (Lines 21-23 of the corresponding PCT publication WO 00/32189 (hereinafter the '189 pub.).

Applicants are unclear at what point this rejection statement is driving at. In so far as Applicants understand the statement the following comments are offered.

Applicants note that their claims are not limited to a tablet formulation and that such a limitation is wholly unwarranted.

Specifically, lines 21-23 recite

> "The pharmaceutical compositions of the present invention **optionally** comprise one or more pharmaceutically-acceptable binding agents or adhesives as a carrier material, **particularly** for tablet formulations."

Underlining and bold added for emphasis

Applicants submit that it is clear that because the above phrase incorporates the modifier "particularly" the description of the use of binding agents or adhesives is not limited to tablet formulations. In addition, Applicants submit that because the phrase incorporates the modifier "optionally" the description of the use of binding agents or adhesives is optional and therefore the preclusion of the HPC is a valid element of the claim.

Applicants note that new claims 95-153 have been added and they further address the HPC embodiment and that those claims and a discussion of the claims in light of the instant rejections are included herein below.

35 U.S.C. 103(a)

Claims 1-10, 12-75, 84 and 86-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Franson et al. US 5,591,456, in view of Black EP 0 863 134 and AAPS Annual Meeting Contributed Papers Abstracts (AAPS).

The rejection states that Franson teaches a dispersible particle comprising crystalline NSAID having hydroxypropyl cellulose adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 1000 nm, and at least 99% of the particle has size less than 400 nm (abstract; and column 3, lines 56 through column 4, lines 1-4).

The rejection also states that Franson does not teach the claimed NSAID compound, such as celecoxib. The rejection states Black teaches a compound useful as a Cox-2 inhibitor for pain relief, fever and inflammation of a variety symptoms disclosed on page 3, lines 29-36. The rejection states that the compound can be administered orally in the form of tablets, troches, lozenges, or capsules (page 4, lines 1-12). The rejection states that the tablets comprise active ingredient in admixture with excipients, e.g., diluents, disintegrants, binding agents, wetting agents, and surfactant (page 4, lines 15-38). The rejection states that the active agent is present in an amount of 10 to 250 mg. The rejection states that the carrier material may vary from about 5 to

about 95% (page 5, lines 39-58). The rejection states that the dosage can be administered once or twice a day, and will provide effective $T_{1/2}$ over a 24 hours period (page 5, lines 22-27). The rejection states that Example 2 discloses the amount of excipients use in a tablet.

The rejection states that it would have been obvious for one of ordinary skill in the art to modify the NSAID formulation of Franson using the COX-2 compound of Black, because Black teaches a COX-2 compound that is proved useful as an alternative to conventional NSAIDs (page 3, lines 41-46), because Black teaches COX-2 as a partial or complete substitute for conventional NSAIDs, and because Franson teaches a particle dispersion suitable for a wide variety of active agents including a number of NSAIDs.

The rejection states that Franson further does not teach the claimed properties, such as bioavailability, C_{max} and T_{max}.

The rejection states that AAPS teaches a celecoxib (Cox-2 inhibitor) formulation that exhibits an unchanged C_{max} value of 1527 and 1077 ng/mL, and a T_{max} of 1.9 hours (see page D32). The rejection states that at page 3469, the AAPS reference teaches a COX-2 composition that is rapidly absorbed with a T_{max} of 1.9 hours, and eliminated with a $t_{1/2}$ of about 15 hours. The rejection states that accordingly, it would have been obvious to one of ordinary skill in the art to optimize the parameter of Franson in view of Black and AAPS to obtain the claimed properties. The rejection states that this is because AAPS teaches properties of a COX-2 formulation that is useful in pharmaceutical art.

The rejection states that Applicant's arguments filed 05/07/10 have been fully considered but they are not persuasive.

The rejection states that Applicant argues that the claimed celecoxib particles are not composite particles. The rejection states that Applicant states that the primary reference Franson et al., mandates a composite particle. The rejection states that Applicants maintain that this is a fundamental difference and it is clear from the quoted passages above from Applicants' specification that Applicants' particles, were they to be composite celecoxib particles, would not provide the advantages of Applicants' claimed composition because Applicants' claimed invention advantages are due at least in part to particulate nature of the celecoxib particles (vs. composite particles).

The rejection states that in response to Applicants' argument that the references fail to show certain features of applicant's invention, it is noted that the feature upon which applicant relies (i.e., celecoxib particles are not composite particles) is not recited in the rejected claim(s). The rejection states that although the claims are interpreted in light of the specification, limitations

from the specification are not read into the claims. See *In re Van Geuns,* 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The rejection also states that Applicant argues that the present claims have been amended to preclude HPC.

The rejection states that although Franson teaches the use of HPC, the purpose of using HPC is to enhance resistant to gastric irritation (See column 3, lines 49-55). Accordingly, the burden is shifted to applicant to show that the presence of HPC would detrimentally affect the desirability for obtaining a composition having high bioavailability. The rejection states that it is of note that Franson teaches a composition that exhibits a high bioavailability (See example 1).

Applicants' 35 U.S.C. 103(a) Response

Applicants traverse the rejection of claims 1-10, 12-75, 84 and 86-90 (as amended) under 35 U.S.C. §103(a) as being unpatentable over Franson et al. US 5,591,456 in view of Black EP 0 863 134 and AAPS Annual Meeting Contributed Papers Abstracts (AAPS) prescribing information, references of record.

Applicants have herein amended the claims in accordance with the implied suggestion by the Examiner. Applicants have herein amended the claims by excluding celecoxib particulates wherein HPC is adsorbed on the particulates (see Page 6, line 30-33 of Applicants' corresponding PCT publication WO 00/32189; hereinafter the '189 pub.). Applicants submit that the amended phrase is fully supported. Applicants further submit that the literal basis for such amendment is not required to be found in the specification (the claim phrase need not be "*in haec verba*" in the specification *In Re Wright* 9 U.S.P.Q.2d 1649, 1651 (Fed. Cir. 1989); *Crowne Operations, Int'l, Inc. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir. 2002). Applicants submit that it is well settled that an inventor may excise the prior art from the claim and still satisfy the written description requirement of section 112, first paragraph *In re Johnson,* 194 U.S.P.Q.187 (C.C.P.A. 1977). Thus, it is a perfectly legitimate procedure for an inventor to claim less than the full scope of his disclosure since it is for an inventor to decide what bounds of protection he will seek (see *In re Wertheim* 191 U.S.P.Q. 90 (C.C.P.A. 1976)). See also In re Driscoll 195 U.S.P.Q. 434 CCPA 1977, which cites the following case.

Engineering Development Laboratories v. Radio Corp. of America, 68 USPQ 238 241-242 (CA2 1946). Judge Learned Hand

> "If, when [applicants] yield any part of what they originally believed to be their due, they substitute a new "invention", only two courses will be open to them: they must at the outset either prophetically divine what the art contains, or they must lay down a barrage of claims, starting with the widest and proceeding by the successive

> incorporation of more and more detail, until all combinations have been exhausted which can by any possibility succeed. The first is an impossible task; the second is a custom already more honored in the breach than in the observance, and its extension would only increase that surfeit of verbiage which has for long been the curse of patent practice, and has done much to discredit it. *It is impossible to imagine any public purpose which it could serve. [Emphasis added]*

A prima facie case of obviousness requires, inter alia, that the cited references teach or suggest every element of the claims. It is respectfully submitted that a prima facie case of obviousness has not been established because the cited references, either alone or in combination, fail to teach or suggest every element of the present claims. As such, the rejection is improper and should be withdrawn. Recently, the Supreme Court in *KSR v. Teleflex, Inc.*, 550 U.S. 398 (2007) has addressed the issue of obviousness and in that case they stated that Courts should still "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does". Applicants submit that this has simply not been done.

First, the MPEP 2143.01 (v) states that the proposed modification cannot render the prior art unsatisfactory for its intended purpose. Restated, if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Yet, this is exactly what the rejection purports to do in reliance on Franson's composite particles (i.e., NSAID having hydroxypropylcellulose adsorbed thereon).

Applicants submit that it is clear from Applicants' specification that the claimed celecoxib particles do not have HPC adsorbed thereon. "Compositions of the present invention contain celecoxib in particulate form. Primary celecoxib particles, generated for example by milling or grinding, or by precipitation from solution, can agglomerate to form secondary aggregate particles." '189 pub. Page 6, line 30-33. This is further reinforced by the following paragraph;

"It has been discovered that milling the celecoxib in an impact mill, such as a pin mill, prior to mixing the celecoxib with excipients to form a composition of the invention, is not only effective in providing improved bioavailability but is also beneficial in overcoming problems associated with the cohesive nature of celecoxib crystals during such mixing or blending." (underline added for emphasis; '189 pub., page 7, lines 12-16).

In contrast, the primary reference Franson et al., mandates a particle having HPC adsorbed thereon. This is a fundamental difference and it is clear from the quoted passages above from Applicants' specification that Applicants' particles, were they to have HPC adsorbed thereon, would not provide the advantages of Applicants' claimed composition because Applicants' claimed

invention advantages are due at least in part to the particulate nature of the celecoxib particles (vs. composite particles).

Further, in the recent CAFC case *In Re Kubin*, 90 USPQ2d 1417 (Fed. Cir. 2009) the court reiterated the requirement for "a suggestion to modify the prior art to practice the claimed invention". Applicants submit that there is simply no motivation in the art cited to exclude celecoxib particles not having HPC adsorbed thereon or that such limitation would result in a product that provides the advantages of "improved bioavailability and overcoming problems associated with the cohesive nature of celecoxib crystals" '189 pub., page 7, lines 12-16. Thus, it is not even obvious to try to modify the prior art formulations to achieve Applicants' claimed invention.

In fact, Franson et al. teaches away from the present invention and specifically mandates the composite nature of the NSAID particles. For example, Franson et al. describes throughout the reference that it is directed to the composite nature of the particles.

In addition, like Franson et al., Black does not teach the claimed compound celecoxib. Rather Black teaches a different COX-2 inhibitor and various compositions thereof. Nowhere does Black describe or suggest the composition of the present claims.

Further, even, assuming arguendo, that there is sufficient motivation to substitute the Cox-2 inhibitor of Black for the naproxen of Franson et al., one would still not achieve Applicants' claimed invention. At least for the reasons that Blacks' Cox-2 inhibitor is not celecoxib and Franson et al. has composite NSAID/hydroxylpropylcellulose particles such a substitution would result in a different product than Applicants' claimed formulation. Thus, with such a substitution (assuming arguendo the proper motivation) one would obtain a formulation comprising composite non-Celecoxib Cox-2 particles having HPC adsorbed on the particle surface.

While one could utilize an additional reference (the AAPS reference) which does contain celecoxib, this necessitates the use of three references to arrive at a formulation comprising composite Celecoxib Cox-2 particles having HPC adsorbed on the particle surface. Clearly, this is still not Applicants' claimed composition.

While the rejection states that "AAPS teaches properties of a COX-2 formulation that is useful in pharmaceutical art" and connects that statement to the optimization of the parameters of Franson et. al./Black, Applicants submit that this does not suggest how to achieve such "properties". Rather what is suggested by the rejection is, at best, a lengthy trial and error involving at least numerous excipients, differing proportions of excipients and potential physical "connection" between the components (e.g., composite). Clearly, the possibilities and even direction of

research to achieve such "properties" is infinite. Further, the reality is that the direction of any research would be towards composite HPC/COX-2 particles

The proper framework for determining *prima facie* obviousness in this case is to consider all of the relevant art, both that relied on by the Examiner and that cited by Applicant. In *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988) the Federal Circuit considered all the prior art, including that cited by the Applicant, and reversed the Board's conclusion of obviousness in a reexamination proceeding.

As applied to the instant application, did the art taken as a whole, including (1) the art considered or relied on by the Examiner and (2) the art and information cited by Applicant, both motivate (without hindsight) one skilled in the art to make the formulation claimed and provide a reasonable expectation of success were that formulation made?

In contrast, to these admonishments, Applicants submit that the rejection improperly selects certain references.

By not taking the art as a whole the rejection improperly focuses on certain research options. Thus, even assuming arguendo that it was obvious to try to modify the prior art formulations, Applicants claimed invention is still not obvious as detailed by *In re Omeprazole Patent Litigation*, 82 U.S.P.Q.2d 1643 (Fed. Cir. 2007). In that case the court found that it would not have been obvious to try applying a water-soluble subcoating as a means of solving a problem. The court cited to the multiple research paths available to one skilled in the art as evidence of unobviousness.

Similarly, in the instant case there are numerous other exemplary formulations described in the NSAID formulation art (this field of art selected by the Examiner) that point towards numerous formulation research pathways. Clearly, the following are just examples and an exhaustive search would highlight the multiplicity of NSAID formulation research paths.

For example, U.S. pat. no. 5,518,738 discloses a formulation comprising a poorly soluble NSAID wherein the crystalline NSAID has polyvinylpyrrolidone adsorbed on the surface in an amount sufficient to maintain an effective average particle size of less than about 1000nm, hygroscopic sugar and sodium lauryl sulfate. This research path points to a NSAID/polyvinylpyrrolidone complex.

Yet another reference is WO 96/21429 which describes formulations (NSAID page 29, lines 6-7) having a microcrystalline cellulose-based excipient having improved compressibility and flowability. The excipient includes silicon dioxide, preferably colloidal silicon dioxide. No mention was made of drug particle size.

Yet another (NSAID column 6, line 58) formulation research pathway is described in U.S. 5,958,452 which describes melt extruded multi-particulate formulation which need not be spheronized. The excipients include hydrophobic materials and hydrophobic fusible carriers. The matrix is cut into multi-particulates having a length of from about 0.1 to about 5 mm.

In yet another example, WO 97/25979 describes a gastrointestinal delivery system comprising a drug (e.g., NSAID page 22, line 21) in combination with a core material, the core being surrounded by a water-insoluble or relatively water-insoluble coating material in which particulate water-insoluble material is embedded. This reference also reviews many other formulations thus emphasizing the numerous NSAID formulation research paths.

Yet another publication is WO 96/35414 which describes formulations (NSAID page 4, 3rd paragraph) for the oral administration of pharmaceutical agents having low water solubility. Those agents are solubilized with a polymer suitable for the formation of nanoparticles, especially from the EUDRAGIT L and S series which release the active agent.

The CAFC has recently reinforced the unobviousness of multiple research pathway options. Thus, even assuming arguendo that it was obvious to try to modify the prior art formulations, Applicants' claimed invention is still not obvious as detailed by *In Re Kubin*. In that case, referring to those situations where obvious to try is equated with obviousness the court stated "The inverse of this proposition is succinctly encapsulated by the Supreme Court's statement in KSR that "where a skilled artisan merely pursues "known options" from a "finite number of identified, predictable solutions," obviousness under 103 arises." *In Re Kubin* at 14

Clearly, Applicants' claimed invention is unobvious since it is not the result of pursuing a known option from a finite number of identified, predictable solutions. The number of possible formulation modifications is extremely large and because of the number and scope of modifications and direction to composite HPC particles, those changes are neither "identified" nor "predictable".

Where the modifications possible were neither finite, identified, or predictable the *In Re Kubin* court admonishes that "in such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *In Re Kubin* at 14

As described above the other exemplary formulations point to the large number of potential formulation modifications and contrast to the admonishments of *In re Kubin* regarding the finite number of identified, predictable solutions.

In Re Kubin also confirmed that the Supreme Court in KSR reinvigorated the CAFC court's requirement that "obviousness does not require absolute predictability of success...all that is required is a reasonable expectation of success". *In Re Kubin* at 16. Applicants submit that there

is simply no reasonable expectation of success that by modifying the prior art example one would have a reasonable expectation of success.

For all the foregoing reasons, Applicants respectfully submit that Franson, Black, and the AAPS reference, alone or in combination, fail to disclose or suggest every element of the present claims. As such, the rejection does not maintain a prima facie showing of obviousness. The rejection of the pending claims (as amended) is therefore improper and should be withdrawn.

New Claims 95-153

New claims 95-153 have been added. These claims include the limitation that celecoxib particulates are not a composite comprising hydroxypropylcelluse absorbed to said celecoxib particulates. The following remarks regarding 35 U.S.C. 112 and 35 U.S.C. 103 relate to new claims 95 – 153 as differentiated from claims 1 – 10, 12 – 75, 84 and 86 – 90.

Specifically, Applicants have herein excluded hydroxypropyl cellulose (HPC) from being adsorbed on the particulate celecoxib (see page 21, line 32 of Applicants' corresponding PCT publication WO 00/32189; hereinafter the '189 pub.). In addition, Applicants have also described the celecoxib particles as being not composite. By "not a composite" is meant that the particulate celecoxib does not have a surface coating that substantially coats the particulate celecoxib. Applicants submit that it is clear from Applicants' specification that the claimed celecoxib particles are not composite particles as defined herein above. "Compositions of the present invention contain celecoxib in particulate form. Primary celecoxib particles, generated for example by milling or grinding, or by precipitation from solution, can agglomerate to form secondary aggregate particles." '189 pub. Page 6, line 30-33; '189 pub., page 7, lines 12-16).

Applicants submit that the phrases are fully supported. Applicants further submit that the literal basis for such amendment is not required to be found in the specification (the claim phrase need not be *"in haec verba"* in the specification *In Re Wright* 9 U.S.P.Q.2d 1649, 1651 (Fed. Cir. 1989); *Crowne Operations, Int'l, Inc. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir. 2002). Applicant submits that it is well settled that an inventor may excise the prior art from the claim and still satisfy the written description requirement of section 112, first paragraph *In re Johnson,* 194 U.S.P.Q.187 (C.C.P.A. 1977). Thus, it is a perfectly legitimate procedure for an inventor to claim less than the full scope of his disclosure since it is for an inventor to decide what bounds of protection he will seek (see *In re Wertheim* 191 U.S.P.Q. 90 (C.C.P.A. 1976)). See also In re Driscoll 195 U.S.P.Q. 434 CCPA 1977, which cites the following case.

Engineering Development Laboratories v. Radio Corp. of America, 68 USPQ 238 241-242 (CA2 1946). Judge Learned Hand

"If, when [applicants] yield any part of what they originally believed to be their due, they substitute a new "invention", only two courses will be open to them: they must at the outset either prophetically divine what the art contains, or they must lay down a barrage of claims, starting with the widest and proceeding by the successive incorporation of more and more detail, until all combinations have been exhausted which can by any possibility succeed. The first is an impossible task; the second is a custom already more honored in the breach than in the observance, and its extension would only increase that surfeit of verbiage which has for long been the curse of patent practice, and has done much to discredit it. *It is impossible to imagine any public purpose which it could serve .[Emphasis added]*

With respect to the rejection's remarks that claim 1 (analogous to new claim 95) did not have binding agent as dependent claim 14 "further comprised binding agents" and claim 23 comprised HPC, Applicants have herein made an effort in New claim set 95-153 to obviate that issue. Applicants note that New dependent claim 107 (analogous to original claim 14) does not have the modifier "further" preceding the recitation of the term "binding agents". In addition, Applicants note that New dependent claim 116 (analogous to original claim 23) does not recite HPC.

In addition, Applicants traverse the Rejection's remark that claim 1 (and accordingly new claims 95-153) is not limited to a tablet formulation and that HPC is a binding agent particularly added for tablet formulations (Lines 21-23 of the corresponding PCT publication WO 00/32189 (hereinafter the '189 pub.).

Applicants are unclear at what point this rejection statement is driving at. In so far as Applicants understand the statement the following comments are offered.

Applicants note that their claims are not limited to a tablet formulation and that such a limitation is wholly unwarranted.

Specifically, lines 21-23 recite

"The pharmaceutical compositions of the present invention **optionally** comprise one or more pharmaceutically-acceptable binding agents or adhesives as a carrier material, **particularly** for tablet formulations."
Underlining and bold added for emphasis

Applicants submit that it is clear that because the above phrase incorporates the modifier "particularly" the description of the use of binding agents or adhesives is not limited to tablet formulations. In addition, Applicants submit that clearly because the phrase incorporates the modifier "optionally" the description of the use of binding agents or adhesives is optional and therefore the exclusion of the HPC is a valid element of the claim.

A prima facie case of obviousness requires, inter alia, that the cited references teach or suggest every element of the claims. It is respectfully submitted that a prima facie case of

obviousness has not been established because the cited references, either alone or in combination, fail to teach or suggest every element of the present claims. As such, the rejection is improper and should be withdrawn. Recently, the Supreme Court in *KSR v. Teleflex, Inc.*, 550 U.S. 398 (2007) has addressed the issue of obviousness and in that case they stated that Courts should still "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does". Applicants submit that this has simply not been done.

First, the MPEP 2143.01 (v) states that the proposed modification cannot render the prior art unsatisfactory for its intended purpose. Restated, if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Yet, this is exactly what the rejection purports to do in reliance on Franson's composite particles (i.e., NSAID having hydroxypropylcellulose adsorbed thereon).

Applicants submit that it is clear from Applicants' specification that the claimed celecoxib particles are not composite particles. "Compositions of the present invention contain celecoxib in particulate form. Primary celecoxib particles, generated for example by milling or grinding, or by precipitation from solution, can agglomerate to form secondary aggregate particles." '189 pub. Page 6, line 30-33. This is further reinforced by the following paragraph;

"It has been discovered that milling the celecoxib in an impact mill, such as a pin mill, prior to mixing the celecoxib with excipients to form a composition of the invention, is not only effective in providing improved bioavailability but is also beneficial in overcoming problems associated with the cohesive nature of celecoxib crystals during such mixing or blending." (underline added for emphasis; '189 pub., page 7, lines 12-16).

In contrast, the primary reference Franson et al., mandates a composite particle. This is a fundamental difference and it is clear from the quoted passages above from Applicants' specification that Applicants' particles, were they to be composite celecoxib particles, would not provide the advantages of Applicants' claimed composition because Applicants' claimed invention advantages are due at least in part to particulate nature of the celecoxib particles (vs. composite particles-see above definition of composite).

Second, the NSAID formulation of the primary reference Franson et al. has HPC adsorbed on the surface of the NSAID composite particle. In fact, Franson et al. mandates the use of HPC as a "surface modifier" "as compared to that of other surface modifiers" (Franson et. al. col. 3, lines 40-44). Clearly, this reference teaches against the use of other "surface modifiers" in contrast to Applicants' claimed invention. In an analogous case, *In re Omeprazole Patent Litigation*, 82

U.S.P.Q.2d 1643 (Fed. Cir. 2007), the references did not disclose or suggest the use of a subcoating in an omeprazole formulation and the court concluded that the formulation was unobvious. Clearly, Franson et al. does not disclose or suggest the use of HPC/surface modifier alternatives and Applicants' claimed formulation is similarly unobvious.

Further, in the recent CAFC case *In Re Kubin*, 90 USPQ2d 1417 (Fed. Cir. 2009) the court reiterated the requirement for "a suggestion to modify the prior art to practice the claimed invention". Applicants submit that there is simply no motivation in the art cited to exclude HPC from the particulates or that such limitation would result in a product that provides the advantages of "improved bioavailability and overcoming problems associated with the cohesive nature of celecoxib crystals" '189 pub., page 7, lines 12-16. Thus, it is not even obvious to try to modify the prior art formulations to achieve Applicants' claimed invention.

In fact, Franson et al. teaches away from the present invention and specifically mandates that such particles must include HPC (and again, mandates the composite nature of the NSAID particles). For example, Franson et al. mandates the use of HPC as a "surface modifier" "as compared to that of other surface modifiers" (Franson et. al. col. 3, lines 40-44) and the whole reference is directed to the composite nature of the particles. Thus, Franson specifically directs that other such agents would not be useful.

Third, like Franson et al., Black does not teach the claimed compound celecoxib. Rather Black teaches a different COX-2 inhibitor and various compositions thereof. Nowhere does Black describe or suggest the composition of the present claims.

Fourth, even, assuming arguendo, that there is sufficient motivation to substitute the Cox-2 inhibitor of Black for the naproxen of Franson et al., one would still not achieve Applicants' claimed invention. At least for the reasons that Blacks' Cox-2 inhibitor is not celecoxib and Franson et al. has composite NSAID/hydroxylpropylcellulose particles such a substitution would result in a different product than Applicants' claimed formulation. Thus, with such a substitution (assuming arguendo the proper motivation) one would obtain a formulation comprising composite non-Celecoxib Cox-2 particles having HPC adsorbed on the particle surface.

While one could utilize an additional reference (the AAPS reference) which does contain celecoxib, this necessitates the use of three references to arrive at a formulation comprising composite Celecoxib Cox-2 particles having HPC adsorbed on the particle surface. Clearly, this is still not Applicants' claimed composition.

While the rejection states that "AAPS teaches properties of a COX-2 formulation that is useful in pharmaceutical art" and connects that statement to the optimization of the parameters of Franson et. al./Black, Applicants submit that this does not suggest how to achieve such

"properties". Rather what is suggested by the rejection is, at best, a lengthy trial and error involving at least numerous excipients, differing proportions of excipients and potential physical "connection" between the components (e.g., composite). Clearly, the possibilities and even direction of research to achieve such "properties" is infinite. Further, the reality is that the direction of any research would be towards composite HPC/COX-2 particles

The proper framework for determining *prima facie* obviousness in this case is to consider all of the relevant art, both that relied on by the Examiner and that cited by Applicant. In *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988) the Federal Circuit considered all the prior art, including that cited by the Applicant, and reversed the Board's conclusion of obviousness in a reexamination proceeding.

As applied to the instant application, did the art taken as a whole, including (1) the art considered or relied on by the Examiner and (2) the art and information cited by Applicant, both motivate (without hindsight) one skilled in the art to make the formulation claimed and provide a reasonable expectation of success were that formulation made?

In contrast, to these admonishments, Applicants submit that the rejection improperly selects certain references.

By not taking the art as a whole the rejection improperly focuses on certain research options. Thus, even assuming arguendo that it was obvious to try to modify the prior art formulations, Applicants claimed invention is still not obvious as detailed by *In re Omeprazole Patent Litigation*, 82 U.S.P.Q.2d 1643 (Fed. Cir. 2007). In that case the court found that it would not have been obvious to try applying a water-soluble subcoating as a means of solving a problem. The court cited to the multiple research paths available to one skilled in the art as evidence of unobviousness.

Similarly, in the instant case there are numerous other exemplary formulations described in the NSAID formulation art (this field of art selected by the Examiner) that point towards numerous formulation research pathways. Clearly, the following are just examples and an exhaustive search would highlight the multiplicity of NSAID formulation research paths.

For example, U.S. pat. no. 5,518,738 discloses a formulation comprising a poorly soluble NSAID wherein the crystalline NSAID has polyvinylpyrrolidone adsorbed on the surface in an amount sufficient to maintain an effective average particle size of less than about 1000nm, hygroscopic sugar and sodium lauryl sulfate. This research path points to a NSAID/polyvinylpyrrolidone complex.

Yet another reference is WO 96/21429 which describes formulations (NSAID page 29, lines 6-7) having a microcrystalline cellulose-based excipient having improved compressibility and

flowability. The excipient includes silicon dioxide, preferably colloidal silicon dioxide. No mention was made of drug particle size.

Yet another (NSAID column 6, line 58) formulation research pathway is described in U.S. 5,958,452 which describes melt extruded multi-particulate formulation which need not be spheronized. The excipients include hydrophobic materials and hydrophobic fusible carriers. The matrix is cut into multi-particulates having a length of from about 0.1 to about 5 mm.

In yet another example, WO 97/25979 describes a gastrointestinal delivery system comprising a drug (e.g., NSAID page 22, line 21) in combination with a core material, the core being surrounded by a water-insoluble or relatively water-insoluble coating material in which particulate water-insoluble material is embedded. This reference also reviews many other formulations thus emphasizing the numerous NSAID formulation research paths.

Yet another publication is WO 96/35414 which describes formulations (NSAID page 4, 3rd paragraph) for the oral administration of pharmaceutical agents having low water solubility. Those agents are solubilized with a polymer suitable for the formation of nanoparticles, especially from the EUDRAGIT L and S series which release the active agent.

The CAFC has recently reinforced the unobvious of multiple research pathway options. Thus, even assuming arguendo that it was obvious to try to modify the prior art formulations, Applicants claimed invention is still not obvious as detailed by *In Re Kubin.* In that case, referring to those situations where obvious to try is equated with obviousness the court stated "The inverse of this proposition is succinctly encapsulated by the Supreme Court's statement in KSR that "where a skilled artisan merely pursues "known options" from a "finite number of identified, predictable solutions," obviousness under 103 arises." *In Re Kubin* at 14

Clearly, Applicants claimed invention is unobvious since it is not the result of pursuing a known option from a finite number of identified, predictable solutions. The number of possible formulation modifications is extremely large and because of the number and scope of modifications and direction to composite HPC particles, those changes are neither "identified" nor "predictable".

Where the modifications possible were neither finite, identified, or predictable the *In Re Kubin* court admonishes that "in such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *In Re Kubin* at 14

As described above the other exemplary formulations point to the large number of potential formulation modifications and contrast to the admonishments of *In re Kubin* regarding the finite number of identified, predictable solutions.

In Re Kubin also confirmed that the Supreme Court in KSR reinvigorated the CAFC court's requirement that "obviousness does not require absolute predictability of success...all that is required is a reasonable expectation of success". *In Re Kubin* at 16. Applicants submit that there is simply no reasonable expectation of success that by modifying the prior art example one would have a reasonable expectation of success.

Applicants submitted an Information Disclosure Statement on December 17, 2010 and request its review.

If the Examiner believes an interview with Applicant's representative would aid in the prosecution of this application, the Examiner is cordially invited to contact Applicant's representative at the number provided below. The points and concerns raised by the Examiner have been fully addressed. Applicants urge that this application is in condition for allowance, which action is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees which may be required and/or credit any overpayments to Deposit Account No. 16-1445.

Respectfully submitted,

Date: 12/17/2010

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